REMARKS

I. Status of the Claims

Claims 1-37 are pending.

Claims 13-15 were previously allowed, but the examiner withdrew allowance.

Claims 16-17 were requested to be included in this group, and the examiner agreed to check whether their non-inclusion was in error, but no decision is in the record. Claims 16-17 were withdrawn by species election. Applicants now request inclusion of claims 16-17.

Claims 1, 3, 5, 9, 11, and 13 are amended.

Claims 4, 10 and 24 are cancelled.

Claims 18-23 and 25-37 are withdrawn.

There were 2 restriction groups in the Office Action mailed November 29, 2006. Claims 1-29 to the composition were elected. Claims 30-37 to the method were withdrawn. The examiner requested a species election and applicant elected "acetaminophen." Therefore, the examiner only prosecuted claims 1-15 (claims 4, 10 and 24 were later cancelled, and claim 30 was amended, although withdrawn). After allowance of claims 13-15, applicant requested adding claims 16-17, because methotrexate was in the allowed claim 13, but that issue is not resolved in the record. Allowance was withdrawn.

II. Interview Summaries

Interviews were held on January 14 and 28, 2009. Participants were Alice O. Martin, Dr. Joel Bernstein, Elaine Ramesh, Examiner Kwon and Supervisor Marschel. On January 28, 2009, Ms. Martin explained that technical difficulties in the January 14, 2009 interview may have contributed to interruptions in the conversation, but expected this problem should be cured by use of a different phone and a conference code.

Claim 1 was discussed, including whether administration of the compounds was limited to occurring together, separately and concurrently, or sequentially. Also dependent claims have different timings, therefore this limitation is defined broadly. The Supervisor expressed his opinion that a claim term was not required for this aspect.

Dr. Bernstein explained that a "composition" was allowed in U.S. Patent No. 5,908,835 in claims 1-4 and in U.S. Patent No. 6,387,936 claims 1-13 without a problem and should be considered a singular entity.

A discussion about the term "consisting essentially of" was that it includes novel and non-obvious components in the specification.

"Hepatotoxic compounds" produce a hepatotoxic effect. "Hepatotoxic compound" is a genus and, as the examiner admits, has a large number of species within it, all enabled in the present specification. (Office Action, May 25, 2007, page 4.) Therefore, applicant should be entitled to claim a "hepatotoxic compound."

The term "about" was discussed.

Kroger (1997), Ogata (US Pat. No. '815) and Murdock (US Pat. No. '788) were discussed in view of 35 U.S.C. §103 rejections.

III. A prima facie case of obviousness is not established

The only remaining rejection is for 35 USC §103.

Claims 1-3, 5-9 and 11-15 were rejected over Kroger (1997), Ogata (US Pat. No. '815) and Murdock (US Pat. No. '788). (Interview Summary, January 6, 2009)

These 3 publications neither singly nor in combination teach all elements of independent claims 1 and 13.

Kroger injected mice intraperitoneally with a combination of nicotinamide and methionine. Doses of 12.5 mg/kg IP were said to provide protection. Activities of GOT + GPT were determined in mice to determine if there were hepatoprotective effects.

The examiner admitted that

> Kroger differs from the claimed invention in the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose.

(Office Action, December 19, 2008, p. 4.)

There are three elements of the pending claims which are not taught by Kroger:

a. Route of administration – In Kroger, nicotinamide or methionine or their combination are administered intraperitoneally ("IP"). This is a very substantive

difference from the routes of administration claimed in the present application. First, IP is virtually never used in humans[1,2] for two principal reasons: (a) IP provides significantly faster and more substantial blood levels of drugs[1,3] than other routes of administration; and (b) risk of infection and local adhesions are unwarranted for use of this route in humans[1] . There are no drugs approved for IP administration to humans in North America or Europe.

b. Composition and Method – In Kroger, nicotinamide and/or methinonine are administered as separate IP injections, and the acetaminophen and methotrexate are administered orally or by IP respectively at an earlier time point. In contrast, in the compositions cited in the pending application, all components (the hepatotoxic active drug agent and the hepatoprotective agents - nicotinamide, methionine, and folic acid) are provided in the same dosage form and administered together in this dosage form (e.g. capsule, tablet, solution).

c. The dosages of nicotinamide and methionine administered IP for protective effects by Kroger are very substantially greater then those administered orally or by injection (but not IP), in the present application. IP dosages used by Kroger range from 25-100 mg/kg nicotinamide and 50-300 mg/kg methionine when each is given alone, to 12.5 mg/kg of each when they are both administered in separate IP injections. Based on the average body weight for adult Americans[4] the dosage of nicotinamide in the claims of the present application ranges from .11 mg/kg to 5.7 mg/kg for males and from .13 mg/kg to 6.7 mg/kg for females, and the dosage of methionine in claims of the present application ranges from .29 mg/kg to 5.7

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1 Goodman & Gilman, "The Pharmaceutical Basis of Therapeutics, "Ninth Edition," 1996, pp. 8-9.
2 Remington's *Pharmaceutical Sciences*, 17th Edition, 1985, p. 784.
3 Gerasimov, M.R. et al., "Comparison Between Intraperitoneally and Oral Methylphenedate Administration, *Pharmacol. Ex. Ther.* 295: 51-57, 2000
4 "National Health and Nutrition Examination Survey, "U.S. CDC National Center for Health Statistics, 2002.

mg/kg for males and from .33 mg/kg to 6.7 mg/kg for females. In contrast, IP injection results in much higher and much faster peak blood levels of drug. In the present application, these dosages are provided orally or by injection **not into** the peritoneum. Consequently, the dosages of nicotinamide and methionine in present claims are minuscule compared to those published by Kroger.

The discussion of these differences renders it clear that the Kroger papers do not teach that much lower dosages of nicotinamide and methionine, administered in a single dosage form with a hepatotoxic drug (e.g. in a capsule, tablet, solution), given by completely different routes of administration than Kroger, would provide safe and effective hepatoprotection from a hepatotoxic drug. The doses in claims 1 and 13 indicate an IP route of administration is not included.

In addition, Table 5, P. 205 of H. Kröger et al. General Pharmacology 33:203-206, 1999 demonstrates that administering 50 mg/kg of nicotinamide intraperitoneally to mice along with 50 mg/kg methotrexate and 50 mg/kg acetaminophen produced significantly higher GOT and GPT elevations (increased liver toxicity) versus mice receiving 50 mg/kg methotrexate plus 50 mg/kg acetaminophen alone. Additionally, Table 5 demonstrates that higher doses of nicotinamide (i.e. 100 mg/kg and 250 mg/kg) given to the mice in conjunction with methotrexate and acetaminophen, while not increasing liver toxicity as did 50 mg/kg of nicotinamide, nonetheless provided no protection against combined methotrexate/acetaminophen-induced liver toxicity. Consequently, Kröger teaches that nicotinamide is non-hepatoprotective at high nicotinamide dosages, and at lower nicotinamide dosages, nicotinamide increases liver damage from methotrexate and acetaminophen. Consequently, Kröger teaches the direct opposite of the present application regarding nicotinamide's protective effects.

Furthermore,

a. The Amendment and Response to the Interview of October 9, 2007 summarized most of the arguments against the publications cited to support obviousness.

b. According to the examiner, Ogata and Murdock are cited for "routine knowledge" of IP, and "routine knowledge" of calculating human dosages from animal studies. The unpredictability of animal testing reported in Exhibits D, E & F indicates that results of clinical studies that are the basis for present claims, are

not obvious over animal studies, and Exhibit H shows IP is not employed for treatment of humans.

i. To demonstrate that known doses of pharmaceutical compositions are not predictable from animal studies, Exhibit D contains a publication regarding the oral animal analgesic study of the proprietary drug civamide and the protocol for the Phase I human study on civamide by Winston Laboratories, Inc. (assignee of the pending application). As can be seen in the publication, in the study utilizing standard analgesic models in animals with oral dosages of 20-200 mg kg civamide, only the 200 mg/kg dose was effective. Since animal dosages bear a very uncertain relationship to human dosages, the Phase I protocol approved by FDA called for single maximum doses of 5 mg or 10 mg, which are approximately equivalent to from 0.063 to 0.126 mg/kg in humans. This is a difference of over 1,000 times less than the animal dosage per kg in the published oral analgesic study. Therefore, human doses were not predictable from animal results.

ii. Exhibit E is a very recent FDA "Guidance on Animal Models." Note lines 108 and 109 which state "the Agency's recognition that many treatments that appeared effective in animals have not proved to be effective in humans."

iii. Exhibit F is a 2007 FDA "Guidance on Drug-Induced Liver Injury" ("DILI"). Note line 99 which states, the "The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals."

iv. Exhibit G is the table Examiner Kwon provided as an authoritative "rule of thumb" to convert animal dosages to human dosages. As Dr. Bernstein pointed out in the recent interviews, this table refers to only surface area conversation factors and thus is relevant (although not accepted by experts in the field) only to topically applied medications, not systemic doses as claimed herein.

v. Exhibit H is composed of discussions of routes of administration of human drugs from Goodman & Gilman "The Pharmacological Basis of Therapeutics" (Ninth Edition) and from the 17th (1985) and 21st (2005)

editions of "Remington's Pharmaceutical Sciences." All of these exhibits make clear that the intraperitoneal route of administration is not employed in human subjects. Additionally, there is not a single drug for intraperitoneal administration approved by the FDA. Goodman & Gilman and Remington are authoritative references in their fields (as opposed to a highly dubious citation from Wikipedia by Examiner Kwon). Therefore Kroger, who used intraperitoneal injections in mice only applied to a mouse model.

A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *To facilitate review, this analysis should be made explicit.*

KSR, 127 S.Ct. at 1740-41 (*emphasis added*). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741.

IV. Terminology Issues Arising During Teleconference

Regarding wording in Claim 1, the examiner stated the breadth of the instantly claimed composition can be construed to include not only a single mixture composition but also a composition where said composition contains ("consisting essentially of") combinations of the specified ingredients at any time from the moment the ingredients are mixed, administered or delivered concurrently, simultaneously or sequentially. Applicants disagree with the Examiner's characterizations of what certain terms in the claims encompass for the following reasons:

a. "A Composition" – Authoritative dictionary references (Exhibit A) demonstrate that a "composition" is a singular entity, though it may be a mixture of individual

ingredients. Additionally, Exhibit B, page 5 of 30, from the USPTO defines the term composition of matter in a way which clearly states this term "relates to chemical compositions and may include mixtures of ingredients as well as new chemical compounds".

b. (Exhibit C) includes a number of recent patents, some approved by Examiner Kwon, some by Supervisor Ardin Marschel, where, "a composition" is used in the claims.

c. "about" – the dictionary definitions (Exhibit A) of "about" are "reasonably close to," "nearly, approximately" and "near to in time, number, quantity, degree, etc." Furthermore, virtually all of the patents in Exhibit C utilize "about" in their description of ranges including Examiner Kwon's recent approvals, and one of Dr. Bernstein's approved by Supervisor Ardin Marschel in 2008.

d. Regarding wording in Claim 9 element (c) - Again this same wording is used in virtually all of the patents in Exhibit C, including the Bernstein Patent No. 7,371,367 approved in 2008 by Supervisor Ardin Marschel. Applicant disagrees that use of the plural could be construed to mean the different ingredients could be administered in separate forms, however, amendments to singular forms are made.

V. Conclusion and Summary

Please allow pending claims. If there are remaining issues, an interview is requested.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41959-102739).

Respectfully submitted,

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Date: April 9, 2009
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